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Comparison of the analgesic effects of transdermal fentanyl and intravenous patient controlled fentanyl after laparotomy

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Abstract

Aim: In our study, we aimed to show whether TDF patch application is effective and acceptable in the management of postoperative pain management.

Material and Methods: In this prospective randomized study, 60 patients, aged between 18-65 years, who had undergone laparotomy, were included in the American Society of Anesthesiologists (ASA) I-II-III, after Gaziantep University local ethics committee approval. No patient was given premedication. The patients were randomly divided into two groups. TDF patch (50µg/hour) was applied to group TDF (n=30) 12 hours before the operation and removed 24 hours after the operation. Group patient-controlled intravenous fentanyl analgesia (PCA) (n=30) was administered postoperatively in the PACU with patient-controlled analgesia with Intravenous fentanyl. When group TDF had pain (VAS 4≥), 100 mg of tramadol was administered as an additional analgesic. Group TDF and Group PCA were clinically observed in the perioperative period.

Results: Resting VAS was statistically significantly better in Group PCA than Group TDF at the 2nd, 4th, 6th, 12th, and 24th hours except the postoperative 1st hour ($p<0.05$). Additional analgesic requirement was statistically higher in group TDF than group PCA at 1st, 2nd, 6th, 12th, and 24th hours except postoperative 4th hour ($p<0.05$).

Discussion: It has been concluded that IV fentanyl and PCA are more effective than TDF in the evaluation of patients in the postoperative period in terms of VAS scores, but TDF can be used as an alternative to patient-controlled analgesia for postoperative analgesia with tramadol support if necessary.

Keywords

Patient-Controlled Analgesia, Pain, Transdermal Fentanyl Patch

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Introduction

One of the important causes of post-surgical anxiety is postoperative pain. Postoperative pain, which starts with surgical trauma and gradually decreases with wound healing, should be relieved quickly and effectively due to undesirable effects such as sympathetic, endocrinological and metabolic changes caused in the postoperative process and the anxiety it causes. A well-provided analgesia will increase the postoperative comfort of the patient, as well as reduce the cost and the development of complications that will lead to a longer stay in the hospital [1].

Various pain management guidelines have been developed for postoperative analgesia in the last 20 years. Patient-controlled analgesia (PCA) method used in postoperative analgesia is a contemporary method that allows the patient to provide self-analgesia. However, the cost of the device and the sets, the need for patient cooperation, the need for the patient and staff to be trained in this regard, limiting mobility and incorrect dose applications may be in question [2, 3].

Transdermal fentanyl administration is an easy and non-invasive procedure. It was studied for postoperative analgesia in the 90s and was not preferred due to its disadvantages such as inability to titrate patient-specific and insufficient in early postoperative analgesia [4, 5]. It is understood that the pharmacokinetic properties of transdermal fentanyl were not taken into account in these studies. In the study conducted by Minville et al. [6], transdermal fentanyl was applied a few hours before the operation, whereas other studies revealed that its effectiveness reached a plateau level in 14 hours and lasted up to 72 hours [7, 8].

In our study, we aimed to compare the analgesic effects of transdermal fentanyl and IV patient-controlled fentanyl after laparotomy.

Material and Methods

None of the patients included in the study wanted to quit the study or were included in then excluded from the study. Sixty patients, aged between 18 and 65, who were evaluated as I-II-III according to the American Society of Anesthesiologists (ASA) classification in the pre-anesthesia evaluation, were included in the study. Patients with kidney and liver failure, patients with cardiac problems, patients with a history of allergy to opioids and the drugs to be administered, pregnant women, patients with opioid dependence, patients with chronic lung disease, patients with dermatological disorders, those with a weight below 50 kg, over 100 kg patients and patients with psychiatric disorders were excluded from the study. The patients were randomly divided into 2 groups: Group TDF (n=30): Patients treated with transdermal fentanyl patch, and Group PCA (n=30): Patients undergoing intravenous (IV) patient-controlled fentanyl analgesia (PCA). After that, the patients were evaluated preoperatively one day before the operation, and written and verbal consent forms were obtained. In Group TDF, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), heart rate (HR), visual analog scale (VAS), Ramsey sedation score (RSS), peripheral oxygen saturation (SpO2) and respiratory rate values were recorded. To patients in the transdermal fentanyl group (Group TDF), 50 µg/h to the anterior chest wall or arm 12 hours before the operation. A tape giving fentanyl (Durogesic 50 µg/h 5TTS Flaster, Johnson & Johnson, Istanbul, Turkey) was applied. The symptoms and signs of nausea, vomiting, bradycardia, dyspnea and itching were recorded in the patients who underwent TDF until the operation. No treatment was given to Group PCA until the operation. Neither group was given any medication or premedication in the preoperative preparation room.

Hemodynamic measurements, sedation scores and VAS values of both groups were recorded in the operating room before induction. Sedation scores of the patients were evaluated with RSS. 2mg/kg propofol (Propofol 1% Fresenius Kabi, İstanbul, Turkey), 1µ/kg fentanyl (Adilat, 0.5mg, 10ml, Vem İlaç, İstanbul, Turkey) for anesthesia induction after preoxygenation (from 10 L/min for 1 min) in the operating room) doses, 0.6 mg/kg intravenous rocuronium bromide (myocron 10 mg, 5ml vial, Vem İlaç Istanbul, Turkey) was administered. Hemodynamic measurements were recorded before and after extubation. In the recovery unit, the duration of the modified Aldrete recovery score (ARS) ≥9 and the sedation scale were evaluated and recorded. After the patients were compiled, they were sent to the relevant service. Side effects such as hemodynamic parameters, RSS, VAS level, nausea, vomiting, pruritus were recorded at postoperative 1, 2, 4, 6, 12 and 24 hours.

In the PCA group, PCA was started with a device (Cadd Legacy 6300 ambulatory infusion pump) with a loading dose of 40 µg, a basal infusion of 20 µg / h, a bolus dose of 40 µg, and a lock-in time of 10 minutes with fentanyl. Amounts of fentanyl consumed were recorded.

Statistical analysis

SPSS for Windows v13 package program was used for statistical analysis, and $p<0.05$ was considered statistically significant. Kolmogorov Smirnov test was used to check the conformity of continuous variables with normal distribution. Student's t-test was used for the comparison of normally distributed variables in 2 independent groups, and Mann Whitney U Test was used for non-normally distributed variables. The single-sample Z test was used in order not to compare the population value versus the sample. Analysis of variance with repeated measures was used in the analysis of data with more than two repeated measures. The relationship between categorical variables was tested with χ^2 analysis. Frequency, percentage and mean±SD values are given as descriptive statistics.

Ethical Approval

This study was approved by the Ethics Committee of Gaziantep University, Faculty of Medicine (Date: 18/12/2012, No: 460). Informed written consent was obtained from the patients for this prospective randomized study. It was carried in Gaziantep University Şahinbey Training Research and Application Hospital Operating Room.

Results

60 randomized clinical trials patients were included in and completed the study. Demographic data are shown in Table 1. When these data were analyzed statistically, no significant difference was found between the groups ($p>0.05$). There was no significant difference between the groups in pre-induction and intraoperative measurements in terms of hemodynamic

parameters such as SAP, DAP, MAP, CAD, and SPO2 (p> 0.05).

When MAP and CAD, which are among the postoperative hemodynamic parameters of the patients, were examined, no significant difference was found between the groups (p>0.05).

When the postoperative peripheral oxygen saturations of the patients were evaluated, no significant difference was observed between the groups (p>0.05).

When the postoperative respiratory rates of the patients were evaluated, no significant difference was observed between the groups (p>0.05).

In terms of postoperative VAS values of the patients, there was statistically significant differences between groups at 2nd hour (p=0.001), 4th hour (p=0.001), 6th hour (p=0.001), 12th hour (p=0.001), and 24th hour (p=0.001). It was lower in Group PCA (Table II). It was lower in Group PCA (Table 2).

The time for the Aldret recovery score (ARS) to be 9 was statistically higher in Group TDF (p=0.001) (Table 3). There was no statistically significant difference between the two groups in terms of postoperative RSS, nausea, vomiting and pruritus data (p>0.05). There was a statistically significant difference in the postoperative additional analgesic consumption at the 1st, 2nd, 6th, 12th, and 24th hours, excluding the postoperative 4th hour (p=0.001).

Postoperative total fentanyl consumption of the patients was statistically higher in group PCA at 1st-2nd-4th-6th hours compared to group TDF (p=0.001). At the 12th and 24th hours postoperatively, group TDF was higher than group PCA (p=0.001).

Table 1. Comparisons of demographic data of the groups

	Group PCA (n=30) Mean ± SD	Group TDF (n=30) Mean ± SD	p value
Age (years)	48,00 ± 11,26	44,40 ± 13,31	0,457
Gender (F/M)	15/15	15/15	1
BMI	24,83 ± 2,92	24,90 ± 2,49	0,925
Operation Type			
Stomach CA	10	11	0,948
Colon CA	9	8	0,948
Intra-abdominal mass	11	11	0,948
Operation time (Min.)	196,00 ± 45,07	201,00 ± 31,66	0,621
ASA (II / III)	13/17	14/16	0, 925

Table 2. Comparisons of postoperative VAS values of the groups

	Group PCA (n=30) Median (Min.-Max.)	Group TDF (n=30) Median (Min.-Max.)	p value
1. hour	3 (4-7)	5 (5-10)	0,235
2. hours	3 (3-6)	6 (4-10)	0,001
4. hours	2 (2-4)	5 (3-8)	0,001
6. hours	2 (1-3)	4 (2-8)	0,001
12. hours	1 (1-2)	4 (2-6)	0,001
24. hours	1 (1-2)	3 (1-4)	0,001

* Statistically significant difference when the two groups are compared.

Table 3. Comparison of Aldret time and postoperative nausea and vomiting values of the groups.

	Group PCA (n=30) Mean ± SD	Group TDF (n=30) Mean ± SD	p value
Aldret time	10,60 ± 3,53	14,16 ± 2,52	0,001
Nausea - vomiting	1,76 ± 0,43	1,73 ± 0,44	0,77

* Statistically significant difference when the two groups are compared.

Discussion

In our study in which we compared the postoperative analgesic efficacy of TDF and IV PCA in elective laparotomy, there was no statistically significant difference between the groups in terms of demographic findings, preoperative and postoperative hemodynamic parameters, and RSS. Postoperative VAS values were significantly lower in Group PCA compared to Group TDF at all times except the 1st hour. Postoperative analgesia consumption was significantly lower in Group PCA than in Group TDF at all times except the 4th hour. Total fentanyl consumption was significantly higher in Group PCA than in Group TDF in the first 6 hours.

The transdermal fentanyl method is suggested to be an alternative option for patients who cannot use patient-controlled analgesia, who are not oriented, who are unable to use their hands, and who have difficulty in providing a venous route [9]. However, in studies conducted, it was observed that respiratory depression was observed in patients who were given additional opioids in cases where the TDF patch was insufficient in terms of analgesia [10]. In this study, we preferred to use tramadol as an analgesic drug as a support in cases where analgesia was insufficient due to the risk of respiratory depression.

TDF and placebo groups 8 hours before the operation and removed 24 hours after the operation [11]. Additional analgesia needs of both groups were met with IV PCA fentanyl. Compared to the placebo group, the TDF group had less pain and less need for additional analgesia [11]. In our study, we aimed to compare the effects of transdermal and IV application of fentanyl on postoperative analgesia and to show the feasibility of postoperative use of TDF as an alternative method to PCA IV fentanyl. Minville et al applied PCA analgesia to all groups after the operation and thus compared TDF fentanyl+PCA with placebo patch+PCA. This study leads to an investigation of the effect of TDF on opioid consumption in addition to PCA, rather than investigating the efficacy of TDF alone in the treatment of postoperative pain. That is, these studies investigated the safety and effectiveness of TDF compared to placebo [6]. In our study, we applied TDF to the patient approximately 12 hours before the induction of anesthesia, based on its pharmacokinetic properties. Thus, we designed to evaluate the effect of fentanyl in serum on VAS and sedation scores more healthily and reliably by providing the time required for it to reach its minimum effective concentration.

Since Varvel et al. showed that serum fentanyl level starts to increase in 4-8 hours in transdermal application, it is seen that application of TDF 1-2 hours before or just before surgery will not have a significant effect on hemodynamic and clinical parameters in operations lasting 2-3 hours [12]. In the studies, it is seen that 25 µg, 50 µg and 75 µg hourly doses are used for postoperative analgesia of TDF [13, 14]. In these studies, TDF above 50 µg/h was not preferred because it may cause respiratory depression. Generally, IV morphine was used in addition to PCA TDF in these studies. In our study, we did not

combine TDF and PCA, but used it for postoperative analgesic purposes separately for each group, aiming not to overestimate respiratory depression and other side effects, and to see the effects of using a single drug with two different methods on postoperative analgesia.

Ketene et al. used tramadol as an additional analgesic in their study with 25 µg/hr, 50 µg/hr and placebo patch, looked at total analgesic consumption and found that the analgesic requirement was significantly lower in the 50 µg/hr TDF group [15]. In our study, the postoperative analgesic requirement was 1st-2nd-6th-12th-24th hours in the TDF group. There was no significant difference at the postoperative 4th hour. There was no need for additional postoperative analgesics in Group PCA. In Group TDF, it was observed that additional analgesics were needed at all times except the postoperative 4th hour. In addition, among the studies, there is no standard in terms of removing TDF in the postoperative period. It is usually removed at 24 or 72 hours [4, 15, 16].

A study examining the variation of postoperative VAS values over time proved that pain intensity decreased over time [17]. Another study showed that most patients who underwent surgery experienced severe pain in the first 24 hours [18]. In our study, the fact that the hourly fentanyl consumption in the PCA group in the first 6 hours, which is the acute period, was much higher than in the TDF group and the patients in the TDF group required additional analgesics support these findings. As a result of the studies, both resting and movement VAS values were found to be lower in the TDF group [6, 15, 19]. Contrary to these studies, Minville et al [6], who compared TDF with placebo, showed that the VAS values were lower in the TDF group and therefore more effective.

The opioids we used in the study generally have a sedative effect. Fentanyl, which is stronger than morphine, has a mild sedative effect at low doses (1-2µg/kg), while it causes deep sedation at high doses (50-150 µg/kg). Although different sedation scoring systems were used, no difference was observed between the groups [15, 19, 20].. In our study, we concluded that the sedation values measured in the postoperative period between the TDF group and the PCA group were not statistically different. In our study, when the Aldret recovery score and recovery times were compared, we found that Group PCA was statistically significantly lower than Group TDF. This may be due to the delay in the onset of PCA and the increased plasma fentanyl concentration in Group TDF. There are studies that did not find a statistically significant difference in terms of side effects in the postoperative period [11, 20-22]. Siafaka et al [23] argued that local erythema, Ketene et al [15], nausea, and Miguel et al [21] argued that respiratory depression was more common in the TDF group. According to our results, typical opioid-related side effects were observed in both groups. However, there was no statistically and clinically significant difference between the groups in terms of side effects.

Limitation

The limitations of the study are that it was performed in a single center, and the number of patients is small. However, the study has many strengths such as its prospective nature, low cost, ease of use, and the use of many parameters and scoring scales.

Conclusion

In conclusion, it was concluded that there was no significant difference between TDF and PCA in terms of intraoperative and postoperative hemodynamic monitoring, but patient-controlled analgesia with IV fentanyl was more effective than TDF in the evaluation of VAS in the postoperative period. However, we believe that effective postoperative analgesia will be provided with an additional analgesic such as tramadol when TDF is required as an alternative to patient-controlled analgesia due to its ease of use in postoperative analgesia.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Chen YK, Boden KA, Schreiber KL. The role of regional anaesthesia and multimodal analgesia in the prevention of chronic postoperative pain: a narrative review. Anaesthesia. 2021;76(Suppl 1):8-17.

2. Macintyre PE, Quinlan J, Levy N, Lobo DN. Current Issues in the use of opioids for the management of postoperative pain: A review. JAMA Surg. 2022;157(2):158-66.

3. Schneider A, Hirth M. Pain management in chronic pancreatitis: Summary of clinical practice, current challenges and potential contribution of the M-ANNHEIM classification. Drugs. 2021;81(5):533-46.

4. Rawal N. Current issues in postoperative pain management. Eur J Anaesthesiol. 2016;33(3):160-71.

5. Marchand G, Ware K, Govindan M, Masoud AT, King A, Ruther S, et al. A systematic review and meta-analysis of Intraperitoneal bupivacaine in laparoscopic gynecologic surgery. J Pain Res. 2021;14:2699-707.

6. Minville V, Lubrano V, Bounes V, Pianezza A, Rabinowitz A, Gris C, et al. Postoperative analgesia after total hip arthroplasty: patient-controlled analgesia versus transdermal fentanyl patch. J Clin Anesth. 2008;20(4):280-3.

7. Mitra S, Carlyle D, Kodumudi G, Kodumudi V, Vadivelu N. New Advances in acute postoperative pain management. curr pain headache rep. 2018;22(5):1-11.

8. Glaun GD, Caram AM, Patel N, Sandler HM. Comparison of pain scores in postoperative patients: Intravenous morphine patient-controlled analgesia vs Iontophoretic transdermal fentanyl. cureus. 2016;8(8):1-5.

9. Romualdi P, Santi P, Candeletti S. Alghedon fentanyl transdermal system. Minerva Med. 2017;108(2):169-75.

10. Ishii H, Kokubun H, Tabata KI, Kanai A. Case Reports of Transdermal Fentanyl Patch Administration Difficulties in Cancer Patients with Excess Sweating. J Pain Palliat Care Pharmacother. 2023;37(1):72-7.

11. Lehmann KA, Einnolf C, Eberlein HJ, Nagel R. Transdermal fentanyl for the treatment of pain after major urological operations. A randomized double-blind comparison with placebo using intravenous patient-controlled analgesia. Eur J Clin Pharmacol. 1991;41(1):17-21.

12. Varvel JR, Shafer SL, Hwang SS, Coen PA, Stanski DR. Absorption characteristics of transdermally administered fentanyl. Anesthesiology. 1989;70(6):928-34.

13. Montanari S, Davani L, Terenzi C, Maltoni M, Andrisano V, De Simone A, et al. Fentanyl pharmacokinetics in blood of cancer patients by Gas Chromatography - Mass Spectrometry. J Pharm Biomed Anal. 2022;219(9):1-4.

14. Zhou J, Curd L, Lohmer LRL, Delpratt N, Ossig J, Schippers F, et al. A population pharmacodynamic Markov mixed-effects model for determining remimazolam-induced sedation when co-administered with fentanyl in procedural sedation. Clin Transl Sci. 2021;14(4):1554-65.

15. Ketene A. Postoperatif ağrıda transdermal fentanil kullanımı. Ankara Sağlık Hizmetleri Dergisi. 2004;6(2):9-16.

16. Kaye AD, Menard BL, Ehrhardt KP, Gennuso SA, Okereke EC, Tirumala SR, et al. Consensus perioperative management best practices for patients on transdermal fentanyl patches undergoing surgery. Curr Pain Headache Rep. 2019;23(7):50-5.

17. Arshad Z, Prakash R, Gautam S, Kumar S. Comparison between transdermal

buprenorphine and transdermal fentanyl for postoperative pain relief after major abdominal surgeries. J Clin Diagn Res. 2015;9(12):1-4.
18. Yoshino K, Nishiumi N, Masuda R, Saito Y, Iwazaki M, Mikami M, et al. [A case of pain management using transdermal fentanyl patches for peritoneal carcinomatosis in a patient with small intestine stoma]. Gan To Kagaku Ryoho. 2011;38(2):325-7.
19. Sevarino FB, Sinatra RS, Paige D, Silverman DG. Intravenous ketorolac as an adjunct to patient-controlled analgesia (PCA) for management of postgynecologic surgical pain. J Clin Anesth. 1994;6(1):23-7.
20. Sevarino FB, Paige D, Sinatra RS, Silverman DG. Postoperative analgesia with parenteral opioids: does continuous delivery utilizing a transdermal opioid preparation affect analgesic efficacy or patient safety? J Clin Anesth. 1997;9(3):173-8.
21. Miguel R, Kreitzer JM, Reinhart D, Sebel PS, Bowie J, Freedman G, et al. Postoperative pain control with a new transdermal fentanyl delivery system. A multicenter trial. Anesthesiology. 1995;83(3):470-7.
22. Sandler AN, Baxter AD, Katz J, Samson B, Friedlander M, Norman P, et al. A double-blind, placebo-controlled trial of transdermal fentanyl after abdominal hysterectomy. Analgesic, respiratory, and pharmacokinetic effects. Anesthesiology. 1994;81(5):1169-80.
23. Siafaka I, Rellia P, Argyra E, Iakovidou N, Sykiotis C, Vadalouka A. Pharmacokinetic profile and efficacy of a fentanyl transdermal delivery system for acute postoperative pain after intra-abdominal gynecologic surgery for cancer. Pain Pract. 2004;4(2):98-104.

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